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September 2, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane,
Room 1061
Rockville, MD 20852

RE: Comments on Docket No. 99D-1718: Draft Guidance for Industry on Monoclonal Antibodies Used as Reagents in Drug Manufacturing published in the Federal Register June 24, 1999.

We agree with the approach taken by FDA in this draft guidance to treat biologic agents differently depending on whether the intended use is as a manufacturing regent or as a human drug. This approach is also found in ICHQ6B in the section that addresses the specifications for raw materials and excipients. We, however, strongly encourage FDA to include all biologicals / biotechnology products used as manufacturing reagents under this guidance rather than limiting the guidance to monoclonal antibodies. The same basic concepts of purity and consistency of manufacture apply to other manufacturing reagents such as cell culture reagents, processing enzymes, and ligands, such as proteins A or G, used in chromatography.

We encourage FDA to evaluate the need for this guidance. The draft guidance, as written, lacks focus. It does not clearly articulate guiding principles that can be applied successfully to a variety of reagents and situations. If FDA determines that this guidance is necessary, the revised version should state whether this guidance supercedes the guidance regarding quality expectations for monoclonal antibody manufacturing reagents as addressed in the Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1997).

Overall, we suggest that ICHQ5A[1] guidance adequately describes all aspects of adventitious agent contamination that are covered in this draft guidance. If FDA decides to issue guidance regarding biologic manufacturing agents, it should be brief and should reference the concepts and practices described in ICH Q5A, ICH Q5D and ICH Q6B. Terms and definitions used in FDA guidance should be the same as terms and definitions used in ICH guidance on related topics. Further, the definition of sterilization provided in this guidance is particularly troublesome, and it is technically incorrect in the way it is applied to viral clearance.

Specific comments on the guidance follow and are, as requested, identified by line location within the document.

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[1] International Conference on Harmonization, Note for Guidance on Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin.

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LINE LOCATION	COMMENT
Line 3	Are manufacturing reagents for combination products (not in vitro diagnostics) that are jointly reviewed by CDRH and CDER or CBER covered under this guidance? Lines 2-8 do not indicate whether these products are covered.
Line 7	The guidance should not apply in the same way to IND submissions as it does to BLA or NDA submissions. Manufacturing processes and control strategies are refined during the drug development process. Assurance of patient safety should be of paramount concern during the IND phase with a complete package of information describing the biologic manufacturing reagent developed over time and available at NDA / BLA submission, not at the time of IND submission.

Line 18	The listing of the immunoglobulin classes (in parentheses in the guidance) should either be eliminated or should correctly include ALL immunoglobulin classes. A manufacturer could consider that IgD molecules are not covered by this draft guidance. Also, the description of monoclonal antibodies should be broadened to describe all classes of immunoglobulins, and fragements (including single chains) derived from *in vitro* or *in vivo* recombinant expression technology as well as those prepared using standard hybridoma fusion techniques. In reality, broadening the scope of the document to include all biologic reagents used in manufacture would include these molecules and would be more appropriate.
Line 32 – 56	The scope indicated in the document covers only monoclonal antibodies. Polyclonal antibodies are not covered in the guidance, yet because they are produced in animals they share similar quality issues. In addition, if the polyclonal antibodies are produced in ruminant animals, sheep and goats, TSE concerns are present. Extending the document to cover all biologic manufacturing reagents, and referencing the ICHQ5A guidance and FDA's letters to manufacturers that were published in the Federal Register on August 29, 1994 would be an appropriate way to resolve this issue.
Lines 62-170	Production issues focus primarily on the issue of adventitious agent contamination. It is also important to address the stability of the expression construct in the production cell line beyond the limit of *in vitro* age for production.
Lines 74-77	What is meant by the differentiation between "biological vs pharmaceutical" facility. Is this meant to differentiate facilities which manufacture CDER regulated products from those which manufacture CBER regulated products? Please clarify.
Lines 129-144 and others throughout the document	We suggest that FDA indicate that many of the expression systems for monoclonal antibodies (lymphoblastoid cells, hybridoma cells, CHO cells) do contain endogenous virus. Manufacturing reagents that do not undergo a rigorous, multi-step purification process may contain some residual virus. If these virus are present and introduced into the drug substance manufacturing process streams, the viral clearance evaluation or validation of the drug substance manufacturing process should be adequate to clear adventitous agents potentially introduced from <u>all</u> sources. See also the comments regarding the definition of sterilization in lines 139-140. We suggest the sentence beginning on line 134 be rewritten to read as follows: *In these instances, the downstream steps in the manufacturing process should be validated, using a challenge test, for their capacity to ~~sterilize~~ remove or inactivate potential adventitious agents or contaminants that are introduced by the reagent.*

Line 134	The need for validation of downstream drug substance manufacturing steps and the scope of the validation should consider the nature and quantity of adventitious agents which may potentially be introduced by the monoclonal antibody / biological reagent. This should include evaluation of endogenous / adventitious agents that the cell expression system may contribute. Thus, if a specification for the biological reagent raw material is, for example, a non-detectable level of virus as determined by appropriate testing, then the need for validation of downstream processing may be minimized and may be addressed by including appropriate model viruses in activation / removal studies. Use of a biological reagent in cell culture should be considered different from the situation where a biological reagent is used in a process step other than cell growth and recovery where adventitious agents could potentially replicate. It may be appropriate to also set specifications for bioburden and endotoxin testing of the biological reagent. The viral validation studies should take into account the biological reagent and its intended use in the pharmaceutical manufacturing process. In many cases, literature data may be an acceptable substitute for actual validation. This may be particularly appropriate for microbial expression systems where extremes of pH and organic solvents are used in drug substance manufacture. Sponsors should discuss this approach with FDA.

Line 139 - 140	A burdensome, and technically incorrect, aspect of this guidance document is the definition of sterilization (line 139-140) to mean "...**complete** (emphasis added) inactivation or removal of all potential adventitious agents." Because drug substance manufacture is not a sterile operation, but is performed under bioburden control, we assume the term "sterilization" is meant to apply primarily to virus. Sterilization is an incorrect term to apply to virus inactivation / removal. The terminology and concepts employed to assure viral safety should be consistent with ICHQ5A, Guidance on Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin. Redefinition of the term "sterilization" is an issue of concern to industry for two reasons: 1) The definition is in contrast to the definition of sterility in FDA's 1994 Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products." The 1994 guidance does not call for "complete removal" of adventitious agents to assure sterility but rather states that "A sterility assurance of 10^{-6} or better should be demonstrated for any terminal sterilization process." 2) ICH Q5A specifically states: "The expression of reduction factors as logarithmic reductions in titer implies that, while residual virus infectivity may be greatly reduced, **it will never be reduced to zero**." (emphasis added). Thus, the definition of "sterilization" as provided in this draft guidance which requires "...complete inactivation or removal..." is more restrictive than the approach to viral inactivation and removal described in ICH Q5A. In fact, it is impossible to assure "complete removal" of virus. Thus, if this draft guidance issued, FDA would be sponsor of two guidance documents that are in conflict with each other, one of which (the draft guidance) is technically incorrect. Rather than redefine "sterilization", FDA should apply the principles and terminology of viral inactivation and removal as described in ICHQ5A. The ICH guidance indicates that complementary approaches are employed to assure freedom adventitious agents. The approaches include testing of cell lines and raw materials, assessment of the capacity of the manufacturing process to remove virus and testing of the product for viral contamination at appropriate step(s)in the manufacturing process. Manufacturing reagents should not be expected to meet the more burdensome requirements of "complete inactivation or removal of all infectious agents" as defined in this draft guidance
Line 160	We suggest FDA reference its own letters to manufacturers, published in the Federal Register on August 29, 1994, rather than simply stating that the "...bovine media components should originate from source herds from countries free of ...(BSE)." Also, geographic sourcing of the material used to produce the biological reagent will impact adventitious agent testing, particularly virus testing, that should be performed.

Section B. beginning Line 197	Why is FDA delineating the description of reference standard production / testing for monoclonal antibody manufacturing reagents? This is an increase in regulatory burden beyond what is expected for other biologic manufacturing regents. Manufacturers must ensure that manufacturing reagents meet appropriate specifications. FDA should not focus on the issue of reference standards for monoclonal antibodies or for any other biologic manufacturing agents. FDA should comment on whether they are requesting this because of specific problems within the industry that has created a public health risk, or whether this is a theoretical concern. FDA should not specify how reference standards should be tested. The manufacturer should identify appropriate quality parameters based on the intended use of the reagent. A certificate of analysis should not be required in the application. Other biologic reagents are used during manufacture and certificates of analysis are not required for these materials. Although we agree that appropriate acceptance criteria should be developed and met, implementation of this guidance would increase the regulatory burden for manufacturers. Further, limiting this requirement to a single type of biologic manufacturing reagent (monoclonal antibodies) is not scientifically sound or defensible.
Lines 186 – 188	FDA should focus on the specifications for the biologic manufacturing agent rather than on the production process. It is unclear what FDA means by a "relaxed" process in line 186.
Line 212	We suggest FDA modify the phrase to read: The following tests are ~~typically used~~ potentially useful:
Line 245 – 255	The final statement about "absolute purity" is not clear. It implies a special purity status for manufacturing reagents, but then the section goes on to delineate testing expectations that are very nearly as thorough as would be expected for a therapeutic product.
Section IV beginning Line 284	FDA should reference ICH Q6B, Specifications: Tests Procedures and Acceptance Criteria for Biotechnological / Biological Products addresses specifications for raw materials. The document states that "Biological raw materials or reagents may require careful evaluation to establish the presence or absence of deleterious endogenous or adventitious agents. Procedures...should be accompanied by appropriate measures to ensure that such process-related impurities or potential contaminants arising from their production and use do not compromise the quality and safety of the drug substance or drug product." Thus, this ICH guidance leads the reader to information regarding adventious agents that is presented in ICH Q5A. The level of detail in the draft guidance should be minimized and reference should be made to the appropriate ICH guidance.
Line 268-272	We agree with FDA that validation of virus removal may occur either in manufacture of the reagent itself or in manufacture of the drug substance or drug product.
Line 286-287	Please clarify the concept of "free monoclonal antibodies." We assume this means antibodies in solution as opposed to antibodies coupled to a solid support.
Line 325	The phrase "permitted experimental conditions" should be changed to "designed operational conditions." These studies are performed to validate production performance.
Line 411-413	We suggest that FDA not dictate where stability data for the biological reagent is recorded. Specifically, suggesting that the "stability be specified in the master batch record" is inappropriate. The expiry or retest date and supporting stability data for the biological reagent, as for any raw material, should be available for review upon inspection and should be stored in accordance with corporate policy.
Lines 416-419	We assume that validation of column performance may be performed at reduced scale and is not necessarily evaluated at full commercial scale. This assumes, however, that the scaled down process is representative of the full commercial scale.

In summary, we recommend FDA make the following changes to the draft guidance document:

- FDA should reconsider the need for this guidance. If it is determined to be necessary, FDA should revise this draft guidance document to cover all biological regents used in drug manufacture. Monoclonal antibodies are a subset of biological reagents which may include cell culture medium components, processing enzymes, and chromatography ligands.
- If this guidance is deemed necessary, it should describe general principles that can be applied to all biologic manufacturing reagents. The revised guidance should state that pharmaceutical manufacture should be supported by a control strategy that ensures appropriate quality of *all* raw materials, control of the manufacturing process itself and testing to appropriate limits/specifications for drug substance and drug product. The revised guidance should not repeat specific requirements or considerations that are covered in other guidance such as ICH Q5A[1] or ICH Q5D[2] or ICH Q6B[3]. The concepts described in these ICH documents should cover most all the issues that FDA appears to be attempting to address in the draft guidance. The revised FDA guidance should be brief and should reference, but not repeat, the relevant ICH guidance.
- The level of detail in the revised guidance document should not cover preparation of reference standards, methods of manufacture, specifications and stability. These features are specific to the biological and its intended use.
- FDA should clarify that the same level of detail and viral evaluation study rigor regarding the biologic manufacturing reagent is not required in an IND as is expected in an NDA or BLA.
- FDA should not refer to "sterilization" when describing virus inactivation and removal because it is a technically incorrect term when applied in this manner. Discussions and terminology of viral clearance should be consistent with ICHQ5A, Guidance on Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin. FDA should apply the terminology and principles of virus inactivation / removal described in ICHQ5A where assurance of viral safety is provided by complementary approaches. An integrated control strategy to assure freedom for adventitious agent contamination of the drug product should consider raw material specifications, in-process controls, virus inactivation / removal where appropriate and drug product testing. Manufacturing reagents should not be expected to meet the more burdensome requirements of "complete inactivation or removal of all infectious agents" as defined in this draft guidance.

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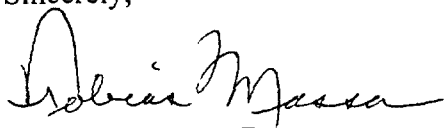
[2] International Conference on Harmonization, Note for Guidance on Quality of Biotechnological / Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological / Biological Products

[3] International Conference on Harmonization, Note for Guidance on Quality of Biotechnological Products: Specifications: Tests Procedures and Acceptance Criteria for Biotechnological / Biological Products (draft of March 10, 1999)

We encourage FDA to continue a dialogue with industry in refining this draft guidance.

Sincerely,



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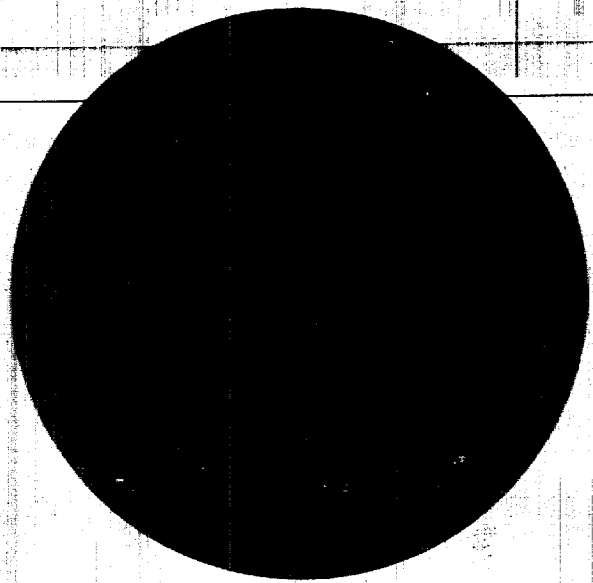

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